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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/402,636	04/26/2000	Richard B. Mazess	17620-9277	6232

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EXAMINER	
HUYNH, PHUONG N	
ART UNIT	PAPER NUMBER
1644	

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3/

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/402,636	MASCAX ET AL.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 March 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-6,11,17,18,20-22,42,44,47 and 49-64* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-6,11,17,18,20-22,42,44,47 and 49-64* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *23* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/5/03 has been entered.

2. Claims 2-6, 11, 17-18, 20-22, 42, 44, 47 and 49-64 are pending and are being acted upon in this Office Action.

3. Claim 20 is objected because a comma is missing between osteopontin and estrogen.

4. Claim 42 is objected because the spacing of "1-aminoalkyl-1, 1-bisphosphonate-24-(OH)- D_2". It should have been "1-aminoalkyl-1, 1-bisphosphonate-24-(OH)-D_2".

5. Claim 47 is objected because it depends on canceled claim 46.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 2-6, 11, 17-18, 20-22, 44, 47 and 49-64 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification discloses only a conjugate comprising at least one vitamin D moiety associated with a target molecule moiety having an affinity for a tissue of interest wherein the vitamin D moiety has a formula II as shown on page 11 lines 13-19 bridging page 12 lines 1 to 6 of the specification, wherein said moiety is selected from the group consisting of 1α previtamin D, 1α, 24-$(OH)_2$D2-aminoalkyl, 11α, 25-$(OH)_2$D2-aminoalkyl linked to the hydroxyl group at C-

1, C-3, C-24 and C-25 of said vitamin D moiety and wherein the targeting moiety is bisphosphonate.

The specification does not teach any conjugate comprising any vitamin D moiety as set forth in claims 20, 44 and 59 wherein the vitamin D moiety being associated with any target molecule moiety having an affinity for a tissue of interest such as calcitonin, bisphosphonate, phosphate, polyaspartic acid, any polyglutamic acid, any minophosphosugar, osteonectin, any bone sialoprotein, osteopontin, estrogen, dehydroepiandrosteron (DHEA), any metal ion-amino acid chelate and combination thereof because the vitamin D moiety structure in claims 20, 44 and 59 is not correct. The vitamin D moiety structure as recited in claims 20, 44 and 59 is incorrect because a carbon is missing between the double rings. Applicant is referred to the correct structure on page 11 of the specification. Further, the hydrocarbon chain in the Z group has excessive number of carbons such as 18 carbons, let alone the z group in the undisclosed vitamin D structure having various substitution, unsubstitution, saturated or unsaturated double bonds, as well as branched or unbranched side chain. The specification on page 11 discloses that the Z is a side chain represented by formula (IIIA) and (IIIB) and note that none of the formula has more than 6 carbons.

Stryer *et al* teach that vitamin D moiety has the structure with maximum 25 carbons including the Z group (See enclosed page 569 for structure). The prior art does not teach vitamin D moiety having the structure as set forth in claims 20, 44 and 59 wherein the side chain alone in the Z group has 18 carbons (C1-C18) that is either saturated or unsaturated, substituted or unsubstituted, and straight or branched.

Even if the structure of the vitamin D moiety in claims 20, and 59 is correct, there is insufficient guidance as to which position or carbon on the vitamin D moiety that the targeting moiety is linked to, much less any moiety such as the ones recited in claims 20, 59 or 44 that would deliver the vitamin D to a tissue of interest without toxicity. Further, given the indefinite number of undisclosed vitamin D conjugate comprising any combination and subcombination of targeting moiety, there is insufficient in vivo working examples demonstrating that any of the claimed conjugate is effective for targeting to bone, or malignancy site for treating any vitamin D related disease or tumor. Since the structure of the vitamin D moiety in the independent claims is not enabled, it follows that any conjugate as set forth in claims 2-6, 11, 17-18, 42, 44, 47, 49-53 and 59-64 are not enabled. It also follows that any pharmaceutical composition comprising any undisclosed vitamin D conjugate mentioned above as set forth in claims 20-22, 54-58 are not

enabled. As to claim 18, the term "or their equivalents" has no structure. There is insufficient guidance as to which compound is equivalent to conjugated estrogen. Is the compound equivalent to estrogen's structure or its function?

It is well known that steroid such as testosterone binds to the androgen receptor and preferentially targets the conjugate to muscle rather than bone. Further, there is no in vivo working example demonstrating that *any* conjugate comprising *any* "vitamin D moiety" associated with *any* target molecule moiety such as testosterone would target the conjugate to tissue of interest such as bone for preventing bone loss, much less preventing abnormal growth such as hyperproliferation of any cells.

Bauss *et al* (of record) teach various conjugates such as 17β-estradiol-bisphosphonate conjugates BM 41.0825, BM 41.0871 and BM41.0825 and yet not all conjugates targeting to tissue of interest such as bone using bisphosphonates are effective for preventing bone loss (See abstract, in particular). Bauss *et al* further teach both estradiol and bisphosphonate alone have been shown to inhibit osteoporosis.

Christiansen *et al* (of record) teach various vitamin D in itself such as 1,25-dihydroxycholecalciferol (1,25(OH2)D3) or combined with estrogen for preventing postmenopausal osteoporosis (See Materials and methods, in particular). Christiansen *et al* further teach long-term treatment using vitamin D may cause side effects such as severe hypercalcemia and rental impairment (See page 308, column 1, in particular).

A pharmaceutical composition in the absence of in vivo data are unpredictable for the following reasons: (1) the conjugate may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the conjugate; (2) other functional properties, known or unknown, may make the conjugate unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

As such, further research would be required. See Brenner v. Manson, 383 U.S. 519, 535-36, 148 USPQ 689, 696 (1966), the court indicates that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion". A patent is therefore not a license to experiment. Because the claimed invention is not supported by the disclosure, it is determined that undue experimentation would be required of the skilled artisan to practice the claimed invention.

Applicants' arguments filed 3/5/03 have been fully considered but are not found persuasive.

Applicants' position is that independent claims have been amended to include the structure of the vitamin D moiety (formula II) as disclosed on page 11 of the specification.

However, the vitamin D moiety structure as recited in claims 20, 44 and 59 is incorrect because a carbon is missing between the double rings. Applicant is referred to the correct structure on page 11 of the specification. Further, the hydrocarbon chain in the Z group has excessive number of carbons such as 18 carbons; let alone the z group in the undisclosed vitamin D structure having various substitution, unsubstitution, saturated or unsaturated double bonds, as well as branched or unbranched side chain. The specification on page 11 discloses that the Z is a side chain represented by formula (IIIA) and (IIIB) and note that none of the formula has more than 6 carbons. Applicant's attention is directed to the detailed discussion above to overcome this rejection.

8. Claims 2-6, 11, 17-18, 20-22, 44, 47 and 49-64 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification discloses only a conjugate comprising at least one vitamin D moiety associated with a target molecule moiety having an affinity for a tissue of interest wherein the vitamin D moiety has a formula II as shown on page 11 lines 13-19 bridging page 12 lines 1 to 6 of the specification, wherein said moiety is selected from the group consisting of 1α previtamin D, 1α, 24-$(OH)_2$D2-aminoalkyl, 11α, 25-$(OH)_2$D2-aminoalkyl linked to the hydroxyl group at C-1, C-3, C-24 and C-25 of said vitamin D moiety and wherein the targeting moiety is bisphosphonate.

The specification does not reasonably provide a **written description** of (1) *any* conjugate comprising at least any one vitamin D moiety having the *formula* as set forth in claims 20, 44 and 59, (2) *any* targeting molecule such as *any* amino phosphosugar, *any* bone sialoprotein, *any* conjugated estrogens equivalents, *any* bone morphogenic protein for the claimed conjugate.

Other than the specific formula of vitamin D moiety as disclosed on page 11 of the specification, there is insufficient written description about the formula associated with function as set forth in claims 20, 44 and 59. Applicant is referred to the correct structure on page 11 of

the specification. Further, the hydrocarbon chain in the Z group has excessive number of carbons such as 18 carbons, there is insufficient written description about the structure of the chemical group to be substituted, the location of the double bonds in the unsaturated C1-C18 hydrocarbon chain in the Z group as well as branched or unbranched side chain.

Even if the structure of the vitamin D moiety in claims 20, and 59 is correct, there is inadequate written description about the position or carbon on the vitamin D moiety that the targeting moiety is linked to, much less about the moiety such as the ones recited in claims 20, 59 or 44 that would deliver the vitamin D to a tissue of interest without toxicity. Further, given the indefinite number of undisclosed vitamin D conjugate comprising any combination and subcombination of targeting moiety, there is insufficient written description about the claimed conjugate that is effective for targeting to bone, or to any malignancy site for treating any vitamin D related disease or tumor. Since the structure or formula of the vitamin D moiety in the independent claims is not adequately describe, it follows that any conjugate as set forth in claims 2-6, 11, 17-18, 42, 44, 47, 49-53 and 59-64 are not adequately described. It also follows that any pharmaceutical composition comprising any undisclosed vitamin D conjugate mentioned above as set forth in claims 20-22, and 54-58 are not adequately described. As to claim 18, claim 18 encompasses more than one antiestrogens, conjugated estrogens or their equivalents. Although the term "their equivalents" refers to conjugated estrogens equivalents, the term "conjugated estrogens equivalents" has no structure. Not only there is more than one forms of conjugated estrogen, the equivalent of said conjugated estrogen may or may not be structurally related. Therefore, the structure of the "conjugated estrogens equivalents" in the claimed conjugate is not adequately described.

Further, the specification discloses only six conjugates having one specific targeting moiety such as bisphosphonate linked to the hydroxyl group at C-1, C-3, C-24 and C-25 of said vitamin D such as 1α, 24-$(OH)_2$D2-aminoalkyl, 11α, 25-$(OH)_2$D2-aminoalkyl. Given the lack of a written description of any additional conjugate comprising any vitamin D moiety associated with any target molecule moiety such as *any* amino phosphosugar, *any* bone sialoprotein, *any* conjugated estrogens equivalents, *any* bone morphogenic protein and *any* combination thereof, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.* Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under

the 35 U.S.C. 112, ¶1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicants' arguments filed 3/5/03 have been fully considered but are not found persuasive.

Applicants' position is that independent claims have been amended to include the structure of the vitamin D moiety (formula II) as disclosed on page 11 of the specification.

However, the vitamin D moiety structure as recited in claims 20, 44 and 59 is incorrect because a carbon is missing between the double rings. Applicant is referred to the correct structure on page 11 of the specification. Further, the hydrocarbon chain in the Z group has excessive number of carbons such as 18 carbons, let alone the z group in the undisclosed vitamin D structure having various substitution, unsubstitution, saturated or unsaturated double bonds, as well as branched or unbranched side chain. The specification on page 11 discloses that the Z is a side chain represented by formula (IIIA) and (IIIB) and note that none of the formula has more than 6 carbons. Applicant's attention is directed to the detailed discussion above to overcome this rejection.

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

10. Claim 42 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The "and" in claim 42, last line should have been "or" because the term "and" would include the combinations in at least one of the vitamin D conjugate, rather than combinations of conjugates.

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. Claims 20, 44, 49-51, 53-56, 58-62 and 64 are rejected under 35 U.S.C. 102(b) as being anticipated by US Pat No 5,232,836 (August 1993, PTO 892).

The '836 patent teaches a conjugate comprising at least one vitamin D moiety having the formula identical to the formula shown in instant claims 20 44, and 59 (See column 8, lines 10-36, in particular) wherein the R1 is OH, R is OH (See Y is denotes to OH, column 8, line 30, in particular), Y is a methylene group (=CH2) and t inherently is 1 wherein the reference vitamin D moiety is being associated with a target molecule such as a phosphate or bisphosphate that inherently targets to bone (See claim 1 of '836, in particular). The '836 patent further teaches various vitamin D conjugate such as vitamin D conjugate to proteins, polypeptides, glycoproteins (column 27, line 11-68, column 28, in particular), antibody (column 28 lines 38, in particular), enzyme or radioisotope (See column 28, lines 35-41, in particular). The '836 patent further teaches a pharmaceutical composition comprising the reference conjugate (See column 45-46, in particular). The '836 patent teaches that the conjugate can be linked to the vitamin D moiety at the C1, C-3, C-24 or C25 position (See column 4, lines 19-45, in particular). However, the advantage of linking the any compound at the carbon 11 position of the vitamin D moiety offers the possibility of introducing chosen modifications of vitamin D without interfering directly with the functions of vitamin D (See paragraph bridging columns 28 and 29, in particular) which can targeting to the vitamin D to the specific targets such as immune, cancer, skin, endocrine, and bone (See column 29, line 18-22, in particular). The terms "comprising" and "having" are open-ended. It expands the vitamin D moiety to include the reference vitamin D moiety in the claimed conjugate. Thus, the reference teachings anticipate the claimed invention.

Applicants' arguments and the declaration under 37 C.F.R. § 1.131 by inventors Drs. Richard B. Mazess and Charles W. Bishop filed 3/5/03 have been fully considered but are not found persuasive.

Applicants' position is that (1) the inventors demonstrate that their invention was conceived of at least as early as September 1996 which is prior to the January 15, 1997, the printed publication date of Kobayashi. (2) Independent claims 20, 44 and 59 have been amended to recite the formula of vitamin D moiety.

With respect to the Kobayashi reference, all rejections of Kobayashi reference has been withdrawn in view of the declaration under 37 C.F.R. § 1.131 by inventors Drs. Richard B. Mazess and Charles W. Bishop filed 3/5/03.

However, the '836 patent (August 1993) teaches a conjugate comprising at least one vitamin D moiety having the formula identical to the formula shown in instant claims 20 44, and 59 (See column 8, lines 10-36, in particular) wherein the wherein R1 is OH, R is OH (See Y is denotes to OH, column 8, line 30, in particular), Y is a methylene group (=CH2) and t inherently is 1 wherein the reference vitamin D moiety is being associated with a target molecule such as a phosphate or bisphosphate that inherently targets to bone (See claim 1 of '836, in particular). The term "comprising" or "having" in said amended claims is open-ended. It expands the vitamin D moiety in the claimed conjugate to include additional functional groups to read on the reference conjugates. Further, even if the structure of the vitamin D formula in claims is correct and the claims recite "consisting of", the generic formula of vitamin D on page 11 would still read on the reference conjugate without the specific structure such as the ones shown on page 15-17.

13. Claims 2-6, 11, 17-18, 20, 44, 49-51, 53, 54-56, 58-62 and 64 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 92/14493 publication (September 1992, PTO 892).

The WO 92/14493 publication teaches a pharmaceutical composition comprising a conjugate wherein the reference conjugate comprising vitamin D compounds or its analogs which inherently has the formula as recited in instant claims 20 44, and 59 linked to a targeting moiety such as an estrogen that targets the bone (See claims 1-5, in particular). The WO 92/14493 publication teaches various conjugates such as vitamin D linked a targeting moiety such as anti-estrogen, thyroid hormone, boron or tetracyclines via a connecting group such as a poly-L-Lysine or a bifunctional connector such as ethylene diamine to form a bond therebetween (See page 6, lines 4-30, claim 5, page 8, line 4, in particular). The reference conjugate is useful for intracellular delivery of therapeutic or diagnostic agent (See page 5, line 5-13, in particular). The WO 92/14493 publication teaches the reference conjugate further comprises at least one therapeutic agent such as antibiotics, or enzymes other than vitamin D (See claim 5 of WO 92/14493 publication, in particular). The 1: 1 or equal molar ratio of at least vitamin D to at least one target molecule in claim 2 is within the purview of one skill in the art as taught by the WO 92/14493 publication. Claim 6 is included in this rejection because the reference teaches that the reference conjugate is associated with at least two functional groups and the linker molecules comprises more than one functional group (See page 6, line 10-16, in particular). Thus, the reference teachings anticipate the claimed invention.

Applicants' arguments and the declaration under 37 C.F.R. § 1.131 by inventors Drs. Richard B. Mazess and Charles W. Bishop filed 3/5/03 have been fully considered but are not found persuasive.

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

15. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

16. Claims 11, 17-18, 20, 44, 47, 49, 52, 54, 57, 59-60, and 63 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No 5,232,836 (August 1993, PTO 892) in view of Bauss *et al* (of record, Calcif Tissue Int 59: 168-173, 1996; PTO 892) or Orme *et al* (of record, Bioorg Med Chem Lett 4: 1375-1380, 1994; PTO 892) or WO 92/21355 (December 1992, PTO 892).

The teachings of the '836 patent have been discussed supra. The '836 patent further, teaches that any compound can be linked to the vitamin D moiety at the C1, C-3, C-24 or C25 position (See column 4, lines 19-45, in particular). However, the advantage of linking the any compound at the carbon 11 position of the vitamin D moiety offers the possibility of introducing chosen modifications of vitamin D without interfering directly with the functions of vitamin D (See paragraph bridging columns 28 and 29, in particular) which can targeting to the vitamin D to the specific targets such as immune, cancer, skin, endocrine, and bone (See column 29, line 18-22, in particular).

The claimed invention in claims 18, 20, 44, 47, 49, 52, 54, 57, 59-60, and 63 differs from the teachings of the reference only that the conjugate wherein the targeting molecule is bisphosphate or calcitonin.

The claimed invention in claim 11 differs from the teachings of the reference only that the conjugate wherein the bifunctional connector is an amino acid chelated to the target molecule moiety and linked to the vitamin D moiety via an amide linkage.

The claimed invention in claim 17 differs from the teachings of the reference only that the conjugate further comprises at least one therapeutic agent other than vitamin D moiety conjugated therewith.

Bauss *et al* teach a method of conjugating bone seeking agent such as bisphosphonate and tetracycline with bone preserving agent such as estrogen and other steroids (E2-BPs) (See page 168, column 2, Materials and Methods, Figure 1, in particular). Bauss *et al* teach that estradiol-bisphosphonates conjugates have been shown to have a high affinity for hydroxyapatide of bone and is useful as a bone resorption inhibitor in various metabolic bone disorders (See page 168, column 2, in particular).

Orme *et al* teach a conjugate such as β-estradiol-3-benzoate-17-succinyl-12A-Tetracycline that targets to the tissue of interest such as bone (See page 1375, in particular). The reference steroid moiety such as β-estradiol-3-benzoate is associated with a target moiety such as Tetracycline having an affinity for a tissue of interest such as bone, which is not plasma (See Title, abstract, page 1375, in particular). The reference steroid moiety is associated with the target molecule moiety via a connecting group such as succinate ester which is a bifunctional connector that forms a bond between said steroid moiety and said target molecule moiety (See page 1376, in particular). Orme *et al* teach selective delivery of estrogen to bone tissue could result in a decrease in the side effects of estrogen therapy for the treatment of osteoporosis both by limiting systemic estrogen levels and by reducing the dosage required to achieve effective therapeutic results (See page 1375, second paragraph, in particular).

The WO 92/21355 publication teaches a method for building of bone in a human subject suffering from age-related bone loss comprising administering to a subject a supplement comprising calcitonin which decreases the rates of bone resorption in osteoporotic patients (See page 11, line 29-30, in particular), Vitamin D such as cholecalciferol (D3), ergocalciferol (D2) and its biologically active metabolites and precursors such as 1α, 25 OH(2) vitamin D, where the vitamin D promotes intestinal absorption of calcium, and contributing to plasma calcium

regulation by acting on bone density and stimulate reabsorption of calcium by the kidney while diphosphonates (also known as Didronel, disodium salt of 1-hydroxyethylidene diphosphonic acid EHDP or editronate) which act primarily on the bone (See page 12, Didronel, claims 1, and 4 of WO 92/21355 publication, in particular). The WO 92/21355 publication teaches that bisphosphonates inhibit the formation, growth and dissolution of hydroxyapatite crystals and their amorphous precursors by chemisorption to calcium phosphate surface (See page 12, lines 14-16, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the phosphate or bisphosphate as taught by the '836 patent for the bisphosphonate as taught by Bauss *et al* and the WO 92/21355 publication or the calcitonin as taught by the WO 92/21355 publication or the tetracycline as taught by Orme *et al* in a conjugate comprising a vitamin D moiety associated with bisphosphate or calcitonin or tetracycline as taught by the '836 patent, Bauss *et al,* Orme *et al* and the WO 92/21355 publication. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because the WO 92/21355 publication teaches that Vitamin D promotes intestinal absorption of calcium, and contributing to plasma calcium regulation by acting on bone density and stimulate reabsorption of calcium by the kidney; diphosphonates (also known as Didronel, disodium slat of 1-hydroxyethylidene diphosphonic acid EHDP or editronate) act primarily on the bone (See page 12, Didronel, claims 1, and 4 of WO 92/21355 publication, in particular) while bisphosphonates inhibit the formation, growth and dissolution of hydroxyapatite crystals and their amorphous precursors by chemisorption to calcium phosphate surface (See page 12, lines 14-16, in particular).

The '836 patent teaches that any compound can be linked to the vitamin D moiety at the C1, C-3, C-24 or C25 position (See column 4, lines 19-45, in particular). However, the advantage of linking the any compound at the carbon 11 position of the vitamin D moiety offers the possibility of introducing chosen modifications of vitamin D without interfering directly with the functions of vitamin D (See paragraph bridging columns 28 and 29, in particular) which can targeting to the vitamin D to the specific targets such as immune, cancer, skin, endocrine, and bone (See column 29, line 18-22, in particular). Bauss *et al* teach that estradiol-bisphosphonates conjugates have been shown to have a high affinity for hydroxyapatide of bone and is useful as a

bone resorption inhibitor in various metabolic bone disorders (See page 168, column 2, in particular). Orme *et al* teach selective delivery of estrogen to bone tissue could result in a decrease in the side effects of estrogen therapy for the treatment of osteoporosis both by limiting systemic estrogen levels and by reducing the dosage required to achieve effective therapeutic results (See page 1375, second paragraph, in particular). In re Kerkhoven, 205USPQ 1069 (CCPA 1980), recognized that "It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose ... [T]he idea of combining them flows logically from their having being individually taught in the prior art" (see MPEP 2144.06). Claim 2 is included in this rejection because the vitamin D moiety is conjugated to the target molecule moiety, which is 1:1 ratio. Claim 11 is included in this rejection because N-hydroxy-succinimidyl ester is a good reagent for reaction with Lysine, which is an amino acid that forms an amide linkage through α-amino group or the ε aliphatic amino group. In addition, the N-hydroxy-succinimidyl ester reacts with the carboxyl group or thiol group of Cysteine amino acid residue that can be chelated. Claim 17 is included in this rejection because additional therapeutic agent such as estrogen which is other than vitamin D moiety can be conjugated therewith as taught by Bauss *et al* and Orme *et al* since estrogen therapy has been used for the treatment of osteoporosis, disease related to bone. The term "comprising" or "having" is open ended. It expands the claimed composition to include additional compound such as adjuvant, which reads on the reference composition. Likewise, the term "having" expands the vitamin D moiety to include additional functional groups.

17. Claims 21-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No 5,232,836 (August 1993, PTO 892) in view of Bauss *et al* (of record, Calcif Tissue Int 59: 168-173, 1996; PTO 892) or Orme *et al* (of record, Bioorg Med Chem Lett 4: 1375-1380, 1994; PTO 892) or WO 92/21355 publication (December 1992, PTO 892) as applied to claims 11, 17-18, 20, 44, 47, 49, 52, 54, 57, 59-60, and 63 mentioned above and further in view of US Pat No. 6,309,666 (of record, Oct 2001, PTO 892).

The combined teachings of the '836 patent, Bauss *et al*, Orme *et al* and WO 92/21355 publication have been discussed supra.

The claimed invention in claim 21 differs from the teachings of the references only that the pharmaceutical composition further comprises a differentially degradable coating encapsulating the conjugate for time release delivery of the conjugate.

The claimed invention in claim 22 differs from the teachings of the references only that the pharmaceutical composition further comprises a differentially degradable coating wherein said coating is an enteric coating.

The '666 patent teaches a pharmaceutical preparation in the form of a coated capsule or enteric coating such as gelatin polymer capsule for time release delivery of any kind of medicament such as prednisolone (See entire document, abstract, column 6 lines 66-67 bridging column 7, lines 1-7, column 20, lines 25, in particular). The '666 patent teaches that the time period from the discharge of the pharmaceutical preparation from the stomach till the contents of the hard capsule start to be released can be controlled to any length by selecting the kind and/or amount of polymer(s) used for a low pH soluble polymer film and/or the kind of the acidic substance (See column 3, lines 31-38, in particular). The reference pharmaceutical preparation has the advantage that the contents of the hard capsule can be released quickly and at any desired site of the lower part of the digestive tract (See column 3, lines 39-42, in particular). From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the prednisolone in the polymer capsule for time release delivery as taught by the '666 patent for the a conjugate comprising at least one vitamin D moiety being associated with a targeting moiety such as bisphosphonate, phosphate, tetracycline or calcitonin having an affinity for bone as taught by the '836 patent, Bauss *et al,* Orme *et al* and the WO 92/21355 publication From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because the '666 patent teaches that the enteric coating pharmaceutical preparation has the advantage that the contents of the hard capsule can be released quickly and at any desired site of the lower part of the digestive tract (See column 3, lines 39-42, in particular).

Applicants' arguments and the declaration under 37 C.F.R. § 1.131 by inventors Drs. Richard B. Mazess and Charles W. Bishop filed 3/5/03 have been fully considered but are not found persuasive.

Applicants' position is that (1) the inventors demonstrate that their invention was conceived of at least as early as September 1996 which is prior to the January 15, 1997, the printed publication date of Kobayashi. (2) Independent claims 20, 44 and 59 have been amended to recite the formula of vitamin D moiety.

In response to item 1, with respect to the Kobayashi reference, all rejections using said reference have been withdrawn. However, the '836 patent (August 1993) teaches a conjugate comprising at least one vitamin D moiety having the formula identical to the formula shown in instant claims 20 44, and 59 (See column 8, lines 10-36, in particular) wherein the wherein R1 is OH, R is OH (See Y is denotes to OH, column 8, line 30, in particular), Y is a methylene group (=CH2) and t inherently is 1 wherein the reference vitamin D moiety is being associated with a target molecule such as a phosphate or bisphosphate that inherently targets to bone (See claim 1 of '836, in particular). Further, The WO 92/14493 publication (September 1992) teaches a pharmaceutical composition comprising a conjugate comprising vitamin D compounds or its analogs which inherently has the formula as recited in instant claims 20 44, and 59 wherein the reference vitamin D moiety is linked to a targeting moiety such as an estrogen that targets the bone (See claims 1-5, in particular).

In response to item 1, the term "comprising" or "having" in said amended claims is open-ended. It expands the vitamin D moiety in the claimed conjugate to include additional functional groups to read on the reference conjugates. Further, even if the structure of the vitamin D formula in said amended claims is correct and the claims recite "consisting of", the generic formula of vitamin D on page 11 would still read on the reference conjugate without the specific structure such as the ones shown on page 15-17.

18. Claims 20, 44, 47, 49, 52, 54, 57, 59-60, and 63 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 92/14493 publication (September 1992, PTO 892) in view of US Pat No 5,232,836 (August 1993, PTO 892) and Bauss *et al* (of record, Calcif Tissue Int 59: 168-173, 1996; PTO 892) or Orme *et al* (of record, Bioorg Med Chem Lett 4: 1375-1380, 1994; PTO 892) or WO 92/21355 (December 1992, PTO 892).

The teachings of the WO 92/14493 publication have been discussed supra.

The claimed invention in claims 20, 44, 49, 52, 54, 57, 59-60, and 63 differs from the teachings of the reference only that the conjugate wherein the targeting molecule is bisphosphate or calcitonin.

The claimed invention in claim 47 differs from the teachings of the reference only that the conjugate wherein the bisphosphonate is linked to said vitamin D moiety at a position on the vitamin D moiety which is C-1, C-3, C-24 or C-25.

The '836 patent teaches a conjugate comprising at least one vitamin D moiety having the formula identical to the formula shown in instant claims 20 44, and 59 (See column 8, lines 10-36, in particular) wherein the wherein R1 is OH, R is OH (See Y is denotes to OH, column 8, line 30, in particular), Y is a methylene group (=CH2) and t inherently is 1 wherein the reference vitamin D moiety is being associated with a target molecule such as a phosphate or bisphosphate that inherently targets to bone (See claim 1 of '836, in particular). The '836 patent further teaches that any compound can be linked to the vitamin D moiety at the C1, C-3, C-24 or C25 position (See column 4, lines 19-45, in particular). However, the advantage of linking the any compound at the carbon 11 position of the vitamin D moiety offers the possibility of introducing chosen modifications of vitamin D without interfering directly with the functions of vitamin D (See paragraph bridging columns 28 and 29, in particular) which can targeting to the vitamin D to the specific targets such as immune, cancer, skin, endocrine, and bone (See column 29, line 18-22, in particular).

Bauss *et al* teach a method of conjugating bone seeking agent such as bisphosphonate and tetracycline with bone preserving agent such as estrogen and other steroids (E2-BPs) (See page 168, column 2, Materials and Methods, Figure 1, in particular). Bauss *et al* teach that estradiol-bisphosphonates conjugates have been shown to have a high affinity for hydroxyapatide of bone and is useful as a bone resorption inhibitor in various metabolic bone disorders (See page 168, column 2, in particular).

Orme *et al* teach a conjugate such as β-estradiol-3-benzoate-17-succinyl-12A-Tetracycline that targets to the tissue of interest such as bone (See page 1375, in particular). The reference steroid moiety such as β-estradiol-3-benzoate is associated with a target moiety such as Tetracycline having an affinity for a tissue of interest such as bone, which is not plasma (See Title, abstract, page 1375, in particular). The reference steroid moiety is associated with the target molecule moiety via a connecting group such as succinate ester which is a bifunctional connector that forms a bond between said steroid moiety and said target molecule moiety (See

page 1376, in particular). Orme *et al* teach selective delivery of estrogen to bone tissue could result in a decrease in the side effects of estrogen therapy for the treatment of osteoporosis both by limiting systemic estrogen levels and by reducing the dosage required to achieve effective therapeutic results (See page 1375, second paragraph, in particular).

The WO 92/21355 publication teaches a method for building of bone in a human subject suffering from age-related bone loss comprising administering to a subject a supplement comprising calcitonin which decreases the rates of bone resorption in osteoporotic patients (See page 11, line 29-30, in particular), Vitamin D such as cholecalciferol (D3), ergocalciferol (D2) and its biologically active metabolites and precursors such as 1α, 25 OH(2) vitamin D, where the vitamin D promotes intestinal absorption of calcium, and contributing to plasma calcium regulation by acting on bone density and stimulate reabsorption of calcium by the kidney and diphosphonates (also known as Didronel, disodium salt of 1-hydroxyethylidene diphosphonic acid EHDP or editronate) which act primarily on the bone (See page 12, Didronel, claims 1, and 4 of WO 92/21355 publication, in particular). The WO 92/21355 publication teaches that bisphonates inhibit the formation, growth and dissolution of hydroxyapatite crystals and their amorphous precursors by chemisorption to calcium phosphate surface (See page 12, lines 14-16, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the estrogen in the vitamin D conjugate as taught by the WO 92/14493 publication for the bisphosphate as taught by the '836 patent Bauss *et al* and the WO 92/21355 publication or the calcitonin as taught by the WO 92/21355 publication for a conjugate comprising a vitamin D moiety associated with bisphosphate or calcitonin associated at the C-1, C-3, C-24, C-25 or C-11 position as taught by the '836 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because the WO 92/21355 publication teaches that Vitamin D promotes intestinal absorption of calcium, and contributing to plasma calcium regulation by acting on bone density and stimulate reabsorption of calcium by the kidney; diphosphonates (also known as Didronel, disodium slat of 1-hydroxyethylidene diphosphonic acid EHDP or editronate) act primarily on the bone (See page 12, Didronel, claims 1, and 4 of WO 92/21355 publication, in particular) while bisphonates inhibit the formation, growth and dissolution of hydroxyapatite

crystals and their amorphous precursors by chemisorption to calcium phosphate surface (See page 12, lines 14-16, in particular). The '836 patent teaches that any compound can be linked to the vitamin D moiety at the C1, C-3, C-24 or C25 position (See column 4, lines 19-45, in particular). Bauss *et al* teach that estradiol-bisphosphonates conjugates have been shown to have a high affinity for hydroxyapatide of bone and is useful as a bone resorption inhibitor in various metabolic bone disorders (See page 168, column 2, in particular). Orme *et al* teach selective delivery of estrogen to bone tissue could result in a decrease in the side effects of estrogen therapy for the treatment of osteoporosis both by limiting systemic estrogen levels and by reducing the dosage required to achieve effective therapeutic results (See page 1375, second paragraph, in particular). In re Kerkhoven, 205USPQ 1069 (CCPA 1980), recognized that "It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose ... [T]he idea of combining them flows logically from their having being individually taught in the prior art" (see MPEP 2144.06). Claim 2 is included in this rejection because the vitamin D moiety is conjugated to the target molecule moiety, which is 1:1 ratio. Claim 11 is included in this rejection because N-hydroxy-succinimidyl ester is a good reagent for reaction with Lysine, which is an amino acid that forms an amide linkage through α-amino group or the ε aliphatic amino group. In addition, the N-hydroxy-succinimidyl ester reacts with the carboxyl group or thiol group of Cysteine amino acid residue that can be chelated. Claim 17 is included in this rejection because additional therapeutic agent such as estrogen which is other than vitamin D moiety can be conjugated therewith as taught by Bauss *et al* and Orme *et al* since estrogen therapy has been used for the treatment of osteoporosis, disease related to bone. The term "comprising" or "having" is open ended. It expands the claimed composition to include additional compound such as adjuvant, which reads on the reference composition. Likewise, the term "having" expands the vitamin D moiety to include additional functional groups. The WO 92/14493 publication teaches that the reference conjugate is useful for intracellular delivery of therapeutic or diagnostic agent (See page 5, line 5-13, in particular).

19. Claims 21-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 92/14493 publication (September 1992, PTO 892) in view of US Pat No 5,232,836 (August 1993, PTO 892) and Bauss *et al* (of record, Calcif Tissue Int 59: 168-173, 1996; PTO 892) or Orme *et al* (of record, Bioorg Med Chem Lett 4: 1375-1380, 1994; PTO 892) or WO 92/21355 (December 1992, PTO 892) as applied to claims 20, 44, 47, 49, 52, 54, 57, 59-60, and 63 mentioned above and further in view of US Pat No. 6,309,666 (of record, Oct 2001, PTO 892).

The combined teachings of the WO 92/14493 publication, '836 patent, Bauss *et al*, Orme *et al* and WO 92/21355 publication have been discussed supra.

The claimed invention in claim 21 differs from the teachings of the references only that the pharmaceutical composition further comprising a differentially degradable coating encapsulating the conjugate for time release delivery of the conjugate.

The claimed invention in claim 22 differs from the teachings of the references only that the pharmaceutical composition further comprising a differentially degradable coating wherein said coating is an enteric coating.

The '666 patent teaches a pharmaceutical preparation in the form of a coated capsule or enteric coating such as gelatin polymer capsule for time release delivery of any kind of medicament such as prednisolone (See entire document, abstract, column 6 lines 66-67 bridging column 7, lines 1-7, column 20, lines 25, in particular). The '666 patent teaches the time period from the discharge of the pharmaceutical preparation from the stomach till the contents of the hard capsule start to be released can be controlled to any length by selecting the kind and/or amount of polymer(s) used for a low pH soluble polymer film and/or the kind of the acidic substance (See column 3, lines 31-38, in particular). The reference pharmaceutical preparation has the advantage that the contents of the hard capsule can be released quickly and at any desired site of the lower part of the digestive tract (See column 3, lines 39-42, in particular). From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the prednisolone in the polymer capsule for time release delivery as taught by the '666 patent for the a conjugate comprising at least one vitamin D moiety being associated with a targeting moiety such as bisphosphonate, phosphate, tetracycline or calcitonin having an affinity for bone as taught by the WO 92/14493 publication, the '836 patent, Bauss *et al,* Orme *et al* and the WO 92/21355 publication. From the combined teachings of the

references, it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because the '666 patent teaches that the enteric coating pharmaceutical preparation has the advantage that the contents of the hard capsule can be released quickly and at any desired site of the lower part of the digestive tract (See column 3, lines 39-42, in particular).

20. Claim 42 is free of prior art.

21. No claim is allowed.

22. Any inquiry concerning this communication or earlier communications from the examiner should be directed to "Neon" Phuong Huynh whose telephone number is (703) 308-4844. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

23. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

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